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Case Report

Unilateral optic nerve hypoplasia with asymmetric septum: A case report of unilateral septo-optic dysplasia

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Abstract. Septo-optic dysplasia is an uncommon diagnosis comprised in part of a unique composition of congenital malformations of the central nervous system. It is defined by three principle findings: optic nerve hypoplasia, absence of the septum pellucidum, and clinical pituitary dysfunction. The syndrome may be associated with various cerebral defects including ectopic posterior pituitary, dysgenesis of the corpus callosum, and malformations of cortical development such as schizencephaly. Septo-optic dysplasia has been compared to holoprosencephaly due to the presence of anterior midline defects and is thought to be a less severe form of lobar holoprosencephaly. Certain neuroradiological features may predict clinical outcomes: patients with malformations of cortical development or ectopic posterior pituitary are at higher risk for neurodevelopmental or endocrine dysfunction, respectively. Here we report a case of unilateral optic nerve hypoplasia with asymmetric appearance of the septum pellucidum thought to be due to ipsilateral absence of the septal leaflet in an otherwise healthy infant with exotropia. This is the first case of suspected unilateral septo-optic dysplasia described in the literature.

Keywords: Septo-optic dysplasia, absent septum, unilateral optic nerve hypoplasia

1. Introduction

Septo-optic dysplasia (SOD) is a rare disorder of neuronal development that consists of three findings: optic nerve hypoplasia (ONH), absence of the septum pellucidum, and clinical pituitary dysfunction [1]. Other malformations of the brain may be associated with SOD, including ectopic posterior pituitary, schizencephaly, and midline fusion defects. The neuroradiological findings often have clinical correlates such as developmental delay and poor visual acuity. Most cases of SOD in the literature feature bilateral ONH and a completely absent septum. In this report we describe a unique case of suspected unilateral SOD with an accompanying midline fusion anomaly in the azygous anterior cerebral artery. These findings reflect the close association of optic nerve development and septal leaflet development. Furthermore, this case demonstrates SOD with a known midline fusion anomaly, the azygous anterior cerebral artery. This case raises questions about the origins of SOD and supports the hypothesis that it is caused by a well-timed disruption in the development of closely-related structures.

2. Case Report

The patient is a 16 month-old full term male who presented at birth with a left-sided exotropia. Fundoscopic

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exam revealed left-sided ONH. At 9 months of age the patient received a CT scan to evaluate an incidental acute traumatic injury (fall). This revealed left ONH (Fig. 1) and an asymmetrical septum pellucidum (Fig. 2). MRI of the brain and pituitary were ordered to more thoroughly evaluate these findings. These studies demonstrated reduced caliber of the left optic nerve (Fig. 3) without abnormal T2 signal and a slightly thinned but otherwise normal optic chiasm (Fig. 4). There was a single, enlarged anterior cerebral artery (Fig. 5). The septum pellucidum was located 3 mm off-midline towards the right and situated directly superior to, and continuous with, the right fornix; the left lateral ventricle appeared larger than the right presumably due to the off-midline location of the septum (Fig. 6).

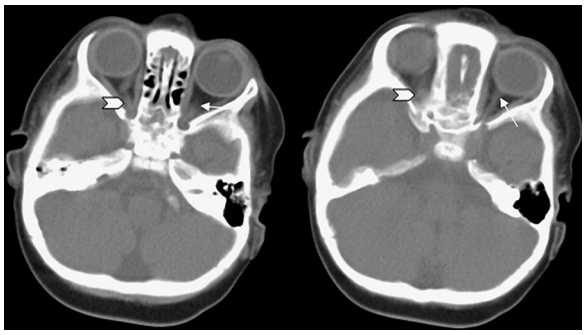

Fig. 1. Axial non-contrast CT images of the brain showing reduced caliber of the left optic nerve (arrow) as compared to the right (arrowhead).

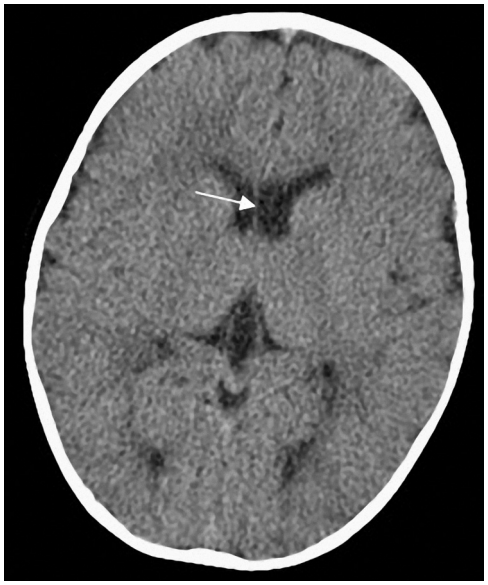

Fig. 2. Axial non-contrast CT scan of the brain showing an asymmetrical septum pellucidum to the right (white arrow).

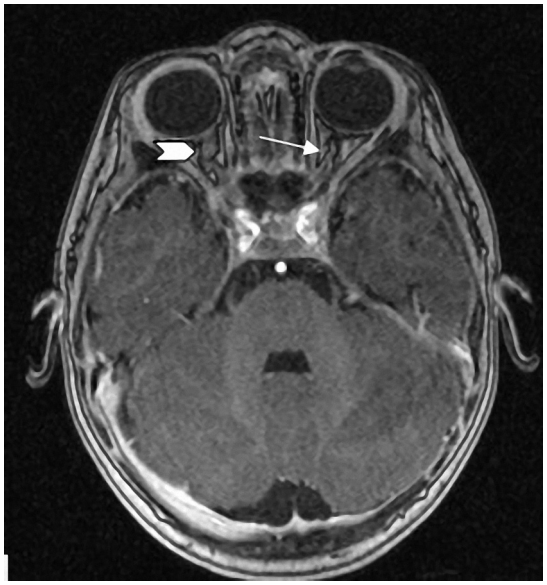

Fig. 3. Axial T1 weighted MRI with contrast showing decreased caliber of the left optic nerve (white arrow) compared to the normal appearance of the right optic nerve (arrowhead). The optic nerves are outlined in India ink.

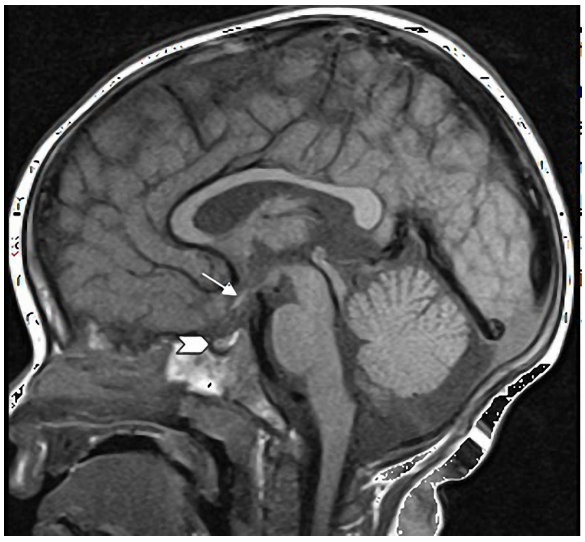

Fig. 4. Sagittal T1 weighted MRI image showing normal appearance of pituitary gland and position of posterior pituitary bright spot (arrowhead). The corpus callosum appears fully formed. The optic chiasm (arrow) is slightly thin.

At 12 months of age, the patient was referred to the pediatric endocrinology clinic to evaluate pituitary

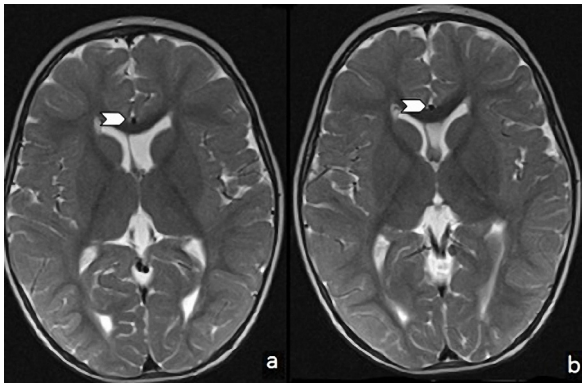

Fig. 5. Axial T2 weighted MRI of the brain showing the septum pellucidum off-midline, favoring the right frontal horn. There appears to be a remnant of the left septal leaflet extending from the fornix to the wall of the ventricle. There is a single, prominent anterior cerebral artery (arrowhead).

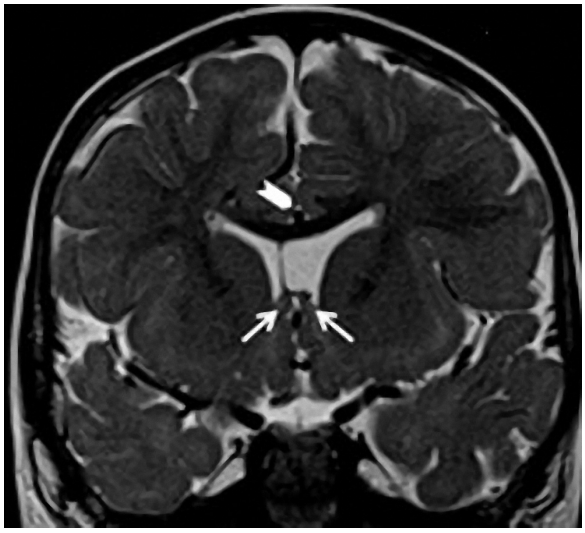

Fig. 6. Coronal T2 weighted MRI image of our patient showing the fornices (arrows) and the close association between the right fornix and the off-midline septum; this likely represents a solitary right septal leaflet with an absent left septal leaflet. A single anterior cerebral artery (arrowhead) is seen, a common feature in disorders involving midline fusion such as SOD and HPE. arrows: fornices, arrowhead: azygous ACA.

function in the setting of ONH. He was meeting his developmental milestones. Physical exam was normal, with bilaterally descended testes and Tanner 1 genitalia; a complete neurological exam revealed no focal deficits. Labs at this time, including TSH, fT4, fT3, IGF-1, cortisol, and prolactin were normal.

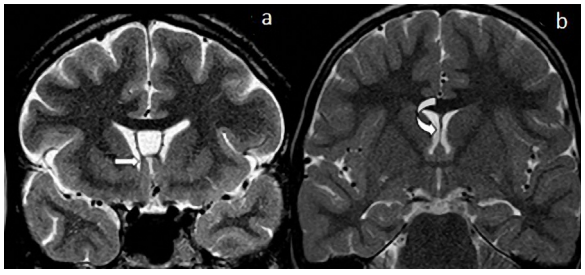

Fig. 7. *a*. Coronal T2 weighted MRI image in a 41 year old patient with incidental persistence of the cavum septum pellucidum showing the left and right septal leaflets associated with the fornices (block arrow). *b*. Coronal T2 weighted MRI image in a 2 year old patient with normal midline septum pellucidum (curved arrow), which is made up of the fused septal leaflets.

At 16 months of age, the patient's height and weight were within normal ranges (45th and 25th percentiles, respectively). He continued to be followed by neurology, ophthalmology, and endocrinology, although he had exhibited no new deficits in any of these systems. As of this review, the patient does not have any endocrine abnormalities, but this does not preclude a diagnosis of SOD. While 62% of patients with SOD have signs of hypopituitarism, only 30% of cases manifest with all three cardinal features [1].

3. Discussion

SOD is an uncommon disorder, but its etiology is not completely understood. It is present in 1 in 10,000 births and affects males and females about equally [2]. One study showed an increased incidence with very young maternal age [2]. SOD may be diagnosed based on certain features elicited when taking a patient history. These key features include: a family history, sensorineural hearing deficits, delays in development, sleep disorders, inability to maintain body temperature, seizures, symptoms suggesting hormonal imbalances, excessive appetite, anosmia, and the presence of other congenital abnormalities [3].

It has been postulated that environmental factors such as drugs and alcohol use during pregnancy may play a role in the development of SOD. Quinine ingestion has been demonstrated to induce optic nerve hypoplasia [4]. A study by Hoyt and Billson also confirmed that phenytoin may cause ONH [5]. Viral infections such as cytomegalovirus may also be responsible for developmental abnormalities of the optic nerve [6].

While most cases of SOD are sporadic, there have been reports of consanguineous familial cases that imply a genetic component [7,8]. Four genes have been implicated in the development of SOD: HESX1, SOX2, SOX3 and OTX2 [9]. Each of these genes has a well-defined role in the development of the central nervous system, and disruption of their expression has produced SOD phenotypes and other CNS malformations in animal models [9]. There are five homozygous and eight heterozygous HESX1 mutations; the heterozygous mutations have been shown to be associated with a milder disease course. SOX2 mutations may cause severe bilateral eye malformations such as anophthalmia. Less than one percent of SOD patients have identified genetic abnormalities. Other factors such as drug/alcohol use and young maternal age must also be considered as factors in SOD pathogenesis [10,11].

Some have theorized that SOD may be the mildest phenotype of holoprosencephaly (HPE) [12], i.e. the failure of the two lobes of the brain to separate completely. This usually occurs during the fifth week of fetal life [13]. The clinical appearance of these patients is similar to SOD: they often have developmental delay and pituitary dysfunction. The three subtypes of HPE, from most mild to most severe, are lobar, semilobar, and alobar. They are distinguished by the degree of fusion of midline structures, such as the basal ganglia and thalami, and the degree of lobation of the cerebral hemispheres [13]. More severe forms of HPE feature an azygous anterior cerebral artery, a finding which was also present in our patient [13].

In discussing this case it is helpful to review normal fetal neuroanatomy. The key structures most commonly affected in SOD are all derived from the anterior neural plate [14]; and not proven, it seems likely that an insult to this structure at key stages of development may result in a phenotype of SOD. Given the diverse phenotypes observed in SOD it is possible that all of these factors play a role and influence one another. During development, the septum pellucidum is composed of two leaflets. The fluid-filled space between these leaflets is commonly called the cavum septum pellucidum (CSP) or more accurately the cavum septi pellucidi. The CSP is a normal structure in fetal development and is often seen in imaging of the fetus and premature infant. On coronal views of the brain the leaflets of the CSP appear intimately associated with the fornices, extending inferiorly from the fornix to the roof of the ventricular system superiorly. In normal development, the CSP is obliterated in a rostral-to-caudal fashion, giving rise to a single septum pellucidum situated in the midline between the two fornices. While this fusion is typically complete by a 40 week gestational term, a CSP can be seen in neonates up to about three months of age [14].

Our case is unique in that it demonstrates an unusual radiographic appearance: an off-midline septum pellucidum with ipsilateral ONH. Bilateral ONH is more common than unilateral (82% vs. 18%) [15]. When ONH is reported with septal abnormalities in the literature, it has been associated with an absent, rather than off-midline, septum pellucidum. While there are a few recent case reports of unilateral optic nerve hypoplasia associated with SOD in the literature, no other authors have described a case with this unique deformity of the septum.

The presumptive explanation for this is concurrent developmental abnormality of the left optic nerve and left septal leaflet. This is feasible given the very close proximity of these two structures both in space and in embryological origin. The human eye begins to form around the fourth week of fetal development and continues to mature throughout the duration of embryogenesis, while the corpus callosum and septal leaflets form around the 11th week and continue to mature until the postpartum period [14]. In combination with the finding of an azygous anterior cerebral artery, a common vascular variant in patients with holoprosencephaly and midline fusion malformations, this patient's imaging suggests unilateral septo-optic dysplasia and the association of SOD with lobar holoprosencephaly. While it is difficult to predict the cause of this embryologic disturbance (i.e. vascular versus genetic abnormality versus sporadic malformation), this unique phenotype continues to suggest the intimate relationship of the optic nerve, septal and midline structures.

Another potential associated feature to be determined by history is stereotypical behavior, such as repeated mannerisms suggestive of an autistic spectrum disorder. Autism and obesity are associated with SOD and may develop after its diagnosis. A study looking at a total of 83 subjects with SOD or ONH found that over half had social, communication, and repetitive/restrictive (SCRR) behavioral difficulties, and over thirty percent had a diagnosed autism spectrum disorder. Therefore, it is recommended that children with SOD receive regular developmental and behavioral evaluations until at least the age of four and a half yr, and children with SOD and SCRR should continue to be monitored after that age [16].

Continuing care for this patient will focus on preserving his visual acuity (measures to correct exotropia as

well as protecting his normal eye), following neurodevelopmental milestones, and continuing to monitor for signs of hypopituitarism. It is unclear whether or not this patient's exotropia is related to his other ophthalmologic issues, as congenital amblyopia is a relatively common finding in otherwise normal neonates. The patient is at a lower risk for neurodevelopmental and endocrine abnormalities because his imaging shows a normal pituitary gland without malformations of cortical development, but these problems often manifest later in life. Whether or not the findings observed in this patient are true signs of central nervous system dysfunction remains to be seen.

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